This Program Announcement expires on October 4, 2004, unless reissued.

ORTHOPAEDIC IMPLANT WEAR

Release Date: September 25, 2001

PA NUMBER: PA-01-141

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Child Health and Human Development

THIS PA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS UP TO $250,000 PER YEAR. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 (REVISION 5/2001) AVAILABLE AT http://grants.nih.gov/grants/funding/phs398/phs398.html.

PURPOSE

The purpose of this Program Announcement (PA) is to encourage the submission of applications for research to enhance our understanding of orthopaedic implant wear. Research to better understand the biology and biomechanics of implant wear, as well as a better understanding of how biomaterial and implant design variables influence repair and how the effects of implant wear can be treated or prevented in the clinical setting is encouraged. Innovative approaches to these scientific areas will be stressed.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS led national activity for setting priority areas. This Program Annoucement(PA), Orthopaedic Implant Wear, is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) research project grant (R01) award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed 5 years. Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts that have been adopted by the NIH. Complete and detailed instructions and information on Modular Grant applications have been incorporated into the PHS 398 (rev. 5/2001). Additional information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm.

RESEARCH OBJECTIVES

Background

Total joint replacement is an effective treatment for relieving pain and restoring function for patients with damaged joints. Approximately 500,000 total hip and knee replacements are performed each year in the United States. These numbers will increase as the population continues to age and as the indications for joint arthroplasty extend to younger patients. For the majority of patients so treated, initial results following surgery are excellent.

Despite this success, implant wear remains the major problem facing the long-term success and survival of these artifical joints. Recent studies have shown that large amounts of minute wear particles are produced by these orthopaedic implants (both metal and plastic), setting into motion a cascade of events that ultimately may result in the disappearance of bone around the implant (osteolysis). This can lead to implant loosening and failure of the artifical joint. Surgery to replace these failures is more difficult to perform, is more costly, and has a poorer outcome than the original joint replacement surgery.

To better understand the clinical, biological, engineering and materials factors that influence the wear process, the NIAMS and the American Academy of Orthopaedic Surgeons (AAOS)

sponsored a scientific workshop entitled “Wear 2000”, in October 2000. This meeting was a follow-up to a jointly sponsored meeting on the same topic in 1995. The primary objective of the most recent workshop was to captitalize on recent scientific discoveries to develop suggestions for future research directions in the area of orthopaedic implant wear. A more detailed description of the proceedings and suggested research needs and opportunities can be obtained from the American Academy of Orthoapedic Surgeons, 6300 North River Road, Rosemont, IL 60018 (http://www.aaos.org).

This PA is an outgrowth of that workshop and of a January 10-12, 2000, NIH Technology Assessment Conference entitled “Improving Medical Implant Performance Through Retrieval Information: Challenges and Opportunities.” A summary of this meeting with conclusions and recommendations can be found at:http://odp.od.nih.gov/consensus/ta/019/019_statement.htm.

Scope

Through the use of this PA, the NIAMS and NICHD anticipate the receipt of a broad range of basic science and translational studies to better understand the biology and biomechanics of implant wear, as well as a better understanding of how biomaterial and implant design variables influence wear and how the effects of implant wear can be treated or prevented in the clinical setting. The following are examples of research topics that are appropriate for this PA; however, they are not to be considered as all inclusive or limiting:

Biology of Implant Wear

Further document the systemic distribution of ions in patients with total joint replacements and correlate this data with patterns of implant wear and degradation.

Test the predictive value of cytokines obtained from serum and synovial fluid with respect to implant wear.

Investigate the role(s) of markers for bone turnover as indicators of implant wear, loosening or failure.

Better understand the role of the osteocyte in response to implant wear debris.

Determine the relative contributions of particles and contaminating endotoxin in aseptic loosening and osteolysis.

Use retrieved tissues with cell models that incorporate multiple cell types exposed to wear particles of clinically relevant sizes, shapes and concentrations to further elucidate the in vivo mechanisms of the biological response to wear particles.

Better understand the potential side effects of systemic distribution of implant wear debris.

Investigate the role(s) of genomic and proteomic analysis to identify patients at risk of developing osteolysis.

Characterize the bioavailablity and bioreactivity of the metal species that have been released from metallic implants.

Standardize hypersensitivity testing modalities and correlate to local tissue response (both in the periprosthetic milieu and in reticuloendothelial storage sites) and clinical outcome.

Biomechanics of Implant Wear

Better understand the mechanisms of total hip and knee replacement wear.

Better understand the wear rates of mobile bearing knee designs and the influences of the effects of bearing surface geometry, component thickness and surface finish on implant wear.

Better understand the role of backside wear in total knee replacement failure.

Develop and validate more accurate techniques to measure in-service wear.

Better understand the role(s) of the initiation and propagation of polyethylene cracks as a function of mixed modes of loading and degradation; develop/better understand, analytical efforts to develop polyethylene failure criteria based upon stress, strain or energy concepts.

Better understand the role(s) of fluid flow, hydrostatic pressure and other mechanical forces in osteolysis.

Implant Materials/Design

Systematically examine the influence of speed, loading cycles and motion directions on a material’s behavior and the resulting wear phenomena.

Better understand the performance of total joint replacement of the shoulder, elbow and ankle. Investigate the use of new forms of polyethylene and the development of new design concepts to improve the life span of these devices.

Better understand the multiaxial mechanical behavior of conventional and cross-linked polyethylenes.

Evaluate the dynamic and time-dependent properties of implant materials and their articulations.

Investigate whether emerging material strategies (e.g., ceramic-to-ceramic, ceramic-to-metal combinations, diamond surface coating and newer cross-linked polyethylenes) diminish wear particle load and inhibit osteolysis.

Develop and validate methods to assess wear in devices with alternative bearing surfaces.

Better understand the role(s) of manufacturing techniques (e.g., casting, grinding, polishing) in adversely altering component dimensions.

Develop and validate sensors and other telemetry devices for the early detection of implant wear-related problems.

Epidemiology, Treatment, and Prevention of Implant Wear Conduct epidemiologic studies to identify the reasons why implant wear is greater in some patients as compared to others.

Develop and validate diagnostic techniques for early detection and quantification of implant wear and its sequela (e.g., edge-detection techniques, three dimensional computation, radiosterometric analysis and newer computed tomographic imaging techniques.

Conduct prospective studies of the relationship between component alignment and wear in total hip and knee replacements.

Develop and validate effective treatments that specifically target biologic processes responsible for osteolysis.

Develop and validate better modes of revision surgery, such as adjuvant forms of osteogenesis for the attachment of components to bone, improved grafting techniques, use of bone substitutes, design improvements, and improvements in surgical technique.

Examine racial and gender differences in implant wear and in the systemic host response to implant wear particles.

Better understand the disparities in the rate of total joint replacements between racial groups.

Extend or develop validated outcome measures to address implant performance and wear.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm: The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and

ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at:http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html are to be used in applying for these grants and will be accepted at the standard application deadlines (http://grants.nih.gov/grants/dates.htm) as indicated in the application kit. This version of the PHS 398 is available in an interactive, searchable PDF format. Although applicants are strongly encouraged to begin using the 5/2001 revision of the PHS 398 as soon as possible, the NIH will continue to accept applications prepared using the 4/1998 revision until January 9, 2002. Beginning January 10, 2002, however, the NIH will return applications that are not submitted on the 5/2001 version. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the application must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application.

This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://grants.nih.gov/grants/guide/notice-files/not98-030.html

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and NIH staff. The research grant application form PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html is to be used in applying for these grants, with modular budget instructions provided in Section C of the application instructions. Applicants are permitted, however, to use the 4/1998 revision of the PHS 398 for scheduled application receipt dates until January 9, 2002. If you are preparing an application using the 4/1998 version, please refer to the step-by-step instructions for Modular Grants available at http://grants.nih.gov/grants/funding/modular/modular.htm. Additional information about Modular Grants is also available on this site.

The title and number of the program announcement must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies in one package to:
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

o The adequacy of the proposed plan to share data, if appropriate.

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o scientific merit (as determined by peer review)
o availability of funds
o programmatic priorities.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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Director, Orthopaedics Program
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Bethesda, MD 20892-6500
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6100 Executive Blvd., 2A03, MSC 7510
Bethesda, MD 20892-7510

Telephone: 301-402-4221
FAX: 301-496-0832
Email: quatranl@exchange.nih.gov

Direct inquiries regarding fiscal matters to:

Ms. Melinda Nelson
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Telephone: (301) 594-3535
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, and portion of a facility) in which regular or routine education, library, day care, health care or early childhood

development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Return to Volume Index
Return to NIH Guide Main Index